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Clinical, Morphological, And Immunolaboratory Characteristics of Types of Chronic Glomerulonephritis Resistant to Pathogenetic Therapy

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Abstract

This review article examines the clinical, morphological, structural, and functional changes, as well as the immunolaboratory characteristics and treatment challenges associated with chronic glomerulonephritis resistant to pathogenetic therapy. It also outlines the fundamental principles for treating refractory glomerulonephritis, alongside research and considerations from recent decades. Furthermore, it identifies various areas of research needed for the treatment of refractory glomerulonephritis.

Keywords: Chronic glomerulonephritis, glucocorticosteroid, immunity, refractory, resistant, lymphocyte.

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1. Introduction

Glomerulonephritis is a disease belonging to a group of pathologies characterized by glomerular damage and immune inflammation. It holds particular social significance due to its high prevalence among young people, especially those of working age [4]. Furthermore, glomerulonephritis (GN) is one of the primary causes of chronic kidney disease (CKD), which ultimately leads to end-stage renal disease (ESRD) and necessitates renal replacement therapy in patients [3]. Determining the cause of chronic glomerulonephritis is not always possible. However, one of the most common etiological causes is group A β-hemolytic streptococcus, which has been studied to arise in the context of chronic infections (tonsillitis, pharyngitis, cholecystitis), as well as frequent hypothermia and weakened immunity. Risk factors also play a significant role in the onset of GN. Exposure to cold, trauma, sunlight, and the repeated use of vaccines, chemicals, and medications can contribute to the development of GN. The presence of chronic infection foci in the body and a weak immune system are certainly important for the disease's progression.

Since the formation of a particular glomerular syndrome is more dependent on the severity of the pathological process and the involvement of certain glomerular structures, rather than on a specific nosological variant of glomerulonephritis, the morphological study of kidney tissue is a crucial stage in modern nephrology for diagnosis and prognosis assessment. Genetic factors also play a significant role in the development of chronic GN. In general, glomerulonephritis is a group of immune-mediated glomerular diseases with varying etiologies, pathogeneses, and prognoses, sharing a common feature of inflammatory proliferation of certain resident glomerular cells.

The majority of GN patients, especially those with nephrotic syndrome (NS), have a relapsing course, and their treatment presents a number of difficulties [4]. In fact, 10-15% of GN patients are considered resistant to oral GCS. Additionally, relapses are observed in 30% of GCS-responsive GN patients with nephrotic syndrome. It should be noted that steroid dependence develops from the repeated use of insufficient doses of GCS and non-compliance with the time and duration standards recommended in guidelines. Steroid resistance, in its steroid-dependent variants, can lead to the development of refractory GN in frequently relapsing or persistent cases. Half of patients with refractory GN progress to the terminal stage of chronic kidney disease (CKD) within 10 years, requiring expensive renal replacement therapies [9]. Typically, regardless of the morphological form of the disease, glucocorticosteroids (GCS) are recommended as the initial treatment for GN presenting with NS, and in cases of relapse, immunosuppressants (mycophenolic acid, calcineurin inhibitors, alkylating agents) and monoclonal antibody drugs are prescribed. In particular, according to the 2021 edition of the international recommendations for the treatment of glomerular diseases [11], rituximab (a selective inhibitor of the immune system's B-cell lineage) in combination with steroids may be the drug of choice when prescribing initial immunosuppressive therapy to GN patients. This allows for the prescription of these drugs without waiting for the results of GCS therapy in patients who are likely to develop steroid resistance to GN. However, there are currently no methods for the early prediction of GN resistance to GCS therapy. This necessitates the search for predictive factors of refractory GN. Therefore, based on the results of studies that have established a link between GN and immunological parameters, research must continue on how the functional characteristics of the immune system influence the nature of the disease's clinical presentation [1, 4].

The development of resistance to glucocorticosteroids (GCS) in these patients, and the various side effects resulting from the subsequent use of immunosuppressants, necessitates the search for new approaches in this area [3]. Current results from experimental studies on animals indicate that the primary mechanism for the development of GN is an imbalance in the ratio of T-helper (Th) subpopulations, specifically Th17 and T-regulatory cells (Treg cells) [8, 20]. The administration of the cytokine interleukin-2 (IL-2) to mice with an experimentally induced model of lupus nephritis led to an increase in the number of Treg cells and a decrease in the accumulation of CD4+ T-cells in the renal tissue [18]. The first successful clinical trials on the use of human recombinant IL-2 (rIL-2) in treating rheumatic diseases have been recognized [16]. However, to date, there is insufficient data on the use of rIL-2 in the treatment of GN [3].

In general, the core of the issue here is refractoriness in glomerulonephritis (GN), that is, resistance to the conducted pathogenetic therapy. One of the most common morphological types of chronic refractory GN is focal segmental glomerulosclerosis (FSGS), which is relatively common from an epidemiological standpoint. FSGS is a type of glomerulopathy that clinically manifests with proteinuria or nephrotic syndrome (NS), characterized by morphologically focal (in individual glomeruli) and segmental (in a specific capillary tuft) sclerosis under light microscopy, and by the effacement of podocyte foot processes under electron microscopy [11]. FSGS is a disease belonging to the "podocytopathies" group, which develops as a result of injury to the visceral epithelial cells (podocytes) of the renal glomeruli. Based on its pathogenetic mechanism, FSGS is divided into primary, secondary, and genetically determined types. Primary FSGS is common, wherein the damage to podocytes is attributed to a circulating "permeability factor." Presumably, these factors cause structural and functional changes in podocytes, characterized by the effacement of foot processes, apoptosis, disruption of the glomerular barrier, detachment from the basement membrane, and the development of proteinuria. Soluble urokinase-type plasminogen activator receptor, cardiotrophin-like cytokine factor 1, CD40, and other factors have been described as potential permeability factors, but their nature is not yet fully understood [6, 13].

The most significant prognostic indicator of renal survival in patients with FSGS is the response to pathogenetic therapy, regardless of the morphological type [19]. Patients who achieve partial or complete remission

have a higher chance of preserving renal function after 10 years (approximately 80% versus < 50% in those with no response). Despite achieving partial remission (incomplete remission), disease progression with deteriorating renal function can still be observed. This indicates either ongoing disease activity or secondary hemodynamic injury: a secondary biopsy may reveal an increased number of sclerosed glomeruli.

In a 2024 study by Kudryashov S.I. and co-authors on this subject, research was conducted in both refractory and non-refractory groups. In all patients, the diagnosis was confirmed either by histomorphological examination of a nephrobioptate or by the presence of anti-PLA2R antibodies in the blood, a marker for membranous nephropathy. The study analyzed the correlation between refractoriness and patient age, the clinical-laboratory picture of GN, and morphological and immunological aspects. According to the findings, patient age was not a significant factor. However, refractoriness was found to be more common in men, in whom the course of NS was accompanied by arterial hypertension and progressive renal dysfunction. These patients exhibited low serum albumin levels and increasing creatinine, which naturally reflected a low GFR in the refractory group. Additionally, the refractory group was observed to have high proteinuria, a pronounced manifestation of NS, and low urinary creatinine excretion [4, 12].

A comparison of immunological parameters in the study groups revealed several characteristics within the T-cell system of immunity in patients with refractory NS. Specifically, an increase was identified in the number of T-lymphocytes of the helper subpopulation, as well as in activated T-lymphocytes expressing HLA-DR antigens. The parameters for cytotoxic T-cell composition did not differ between the groups. However, differences were found in the parameters of the activated subpopulations of this cell population. Thus, in the group of patients with refractoriness, the median values were higher for both cytotoxic cells expressing the HLA-DR antigen and cytotoxic CD38+ cells with high-density expression of the CD8 antigen. It is known that HLA-DR are class II antigens of the human major histocompatibility complex, and the level of their expression on the T-cell surface increases during the late stages of activation [4]. In refractory NS, the number of cytotoxic cells expressing this activation marker is 2.2 times higher than the same indicator in the comparison group of patients. Against a background of high-density CD8 antigen expression, a significant (2.4-fold) increase was observed in the cellular content of the most active subpopulation of cytotoxic T-lymphocytes carrying the CD38 antigen. Lymphocytes of this subpopulation are activated, proliferate, and are considered cytotoxic effector cells [10]. Their increase indicates the activation of T-cell cytotoxicity. An increased immunoregulatory index (T-helpers/cytotoxic T-lymphocytes) was noted in the group of patients with refractoriness. This is due to an increase in the number of T-helper cells against the background of an unchanged number of cytotoxic T-lymphocytes. The results of this study indicate a significant decrease in the number of Treg cells in refractory NS. Changes in Treg cell composition have previously been described in patients with idiopathic NS [16]; these cells are known to be capable of suppressing immune responses to ensure an adequate balance in the immune system's response to foreign and self-antigens. These cells block autoreactive immune processes and the development of autoimmune diseases. Despite their small percentage, they participate in maintaining the immune system in a state of immune tolerance to its own cells and tissues [7], blocking the activity of the effector links of humoral immunity and T-cell-mediated cytotoxicity. Furthermore, they suppress the activity of NK cells, dendritic cells, and macrophages. Treg cells exert their suppressive effect primarily through the production of anti-inflammatory immunosuppressive cytokines—IL-10 and TGF-β [17]. The literature contains reports that Treg cell levels return to normal during NS remission as a result of treatment with GCS or monoclonal antibodies [5].

Significant intergroup differences were detected in most of the studied parameters of the B-cell system of immunity. In patients with refractory GN, the number of B-lymphocytes increased, and the levels of IgM and circulating immune complexes in the system increased against a background of decreased IgG levels compared to the parameters of the comparison group of patients. The identified features of the humoral component of adaptive immunity indicate its significant activation in patients with refractory GN. Activation of the humoral component of the immune system leads to the formation of autoantibodies that bind to the autoantigens of glomerular podocytes. The resulting immune complexes are localized subepithelial, activating the complement system, whose effector components exert a damaging effect on podocytes and lead to increased permeability of the glomerular filter [4]. The decrease in serum IgG levels in patients with refractory GN can be explained by more pronounced damage to the glomerular filter and an increase in its permeability. This increases the excretion of this class of immunoglobulins in the urine. At the same time, IgM and IgA, which have a higher molecular weight than IgG, are lost in the urine to a lesser extent.

Evidence for the involvement of humoral autoimmune mechanisms in the development of GN with NS is the detection of circulating autoantibodies against phospholipase A2 transmembrane 1 receptor (PLA2R1) or thrombospondin type 1 domain-containing 7A (THSD7A) in 70-90% of patients with membranous nephropathy, which is the primary histomorphology variant of NS [14, 15]. Further proof of the importance of humoral mechanisms in the pathogenesis of GN with NS is the successful results of treatment with monoclonal antibodies (rituximab) against CD20+ B-lymphocytes, which are the main cells of humoral immunity [10].

Thus, summarizing our observations from the analysis of the immune status in patients with refractory GN, it was noted that the identified changes in the immune parameters of the T- and B-cell systems (a decrease in the number of Treg cells, an increase in T-cell cytotoxicity, an increase in the number of B-cells, and an increase in IgM and circulating immune complexes) may play a significant role in the development of refractory GN. These analyses also indicate the involvement of immunological mechanisms in the development of refractory GN accompanied by NS. Refractory GN is associated with significant activation of the humoral component of adaptive immunity and a marked imbalance between the immunoregulatory and activating subgroups of T-lymphocytes. This manifests as increased cytotoxic T-cell activity against a background of an increased number of T-helper cells and a decreased level of Treg cells. Most importantly, the level of Treg cells in the blood serum serves as a prognostic indicator, where a low count of these cells (Treg cells <1.9% [4]) indicates a high probability of developing refractory GN accompanied by NS.

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